(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 February 2002 (28.02.2002)

PCT

(10) International Publication Number
WO 02/16545 A2

(51) International Patent Classification[7]: C12M 1/26, B65D 81/32

(21) International Application Number: PCT/GB01/03817

(22) International Filing Date: 24 August 2001 (24.08.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0020909.8 25 August 2000 (25.08.2000) GB
0107268.5 23 March 2001 (23.03.2001) GB

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/16545 A2

(54) Title: STORAGE AND CONVERSION OF COMPOSITIONS

(57) Abstract: A kit for the storage and conversion of a composition, the kit comprising a first vessel (102) containing the composition in a first condition (e.g. inactivated micro-organisms) and being closed by a rupturable seal (113); a second vessel (103) containing a medium for conversion of the composition from the first condition to a second conditions said second vessel being closed by a rupturable seal (113) and a connector member (104) onto which the first and second vessels (102, 103) are assemblable said connector member (104) being adapted to rupture said seal (113) and to provide for communication of the interiors of said first and second vessels.

STORAGE AND CONVERSION OF COMPOSITIONS

The present invention relates to the storage of a composition in a first condition and conversion of that composition into a second condition when required.

The term "composition" used herein includes microorganisms. The "first condition" may for example be an inactive form of the composition and the "second condition" may be an active form thereof.

The invention is applicable particularly, but not exclusively, to the storage of microorganisms in an inactive form and their subsequent conversion to an active form.

Microorganisms may require transport from one laboratory to another, or for example to a culture collection centre. For such transport it is important that the microorganisms are preserved in a dry suspended state (i.e. an inactive form) and that when they reach their destination they may be resurrected into a viable culture (i.e. an inactive form). For preservation during transport, it is generally preferred that microorganisms are freeze dried or lyophilised.

The suspended microorganisms are generally stored in a glass vial that has been sealed with a flame. When the glass vials reach their destination and it is desired to activate the contents, it is necessary to cut open the glass vial, and either to transfer the freeze dried contents to a vessel of resuscitating liquid or to effect resuscitation in situ. Some ampules are very difficult to open and require filing in order sufficiently to weaken the glass so that the ampule can be broken. This presents risks of contamination of the culture through the introduction of contaminants through the filed area of the ampule, as well as risk of injury to the operator, should the ampule unexpectedly break. In addition, there is the risk of injury and inoculation from the broken glass (i.e., the operator may be cut on the edge of the broken glass and be inoculated with the organisms present in the ampule). This is of particular consideration if the organisms are pathogenic.

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It is an object of the present invention to obviate or mitigate the abovementioned disadvantages.

According to the present invention there is provided a kit for the storage and conversion of a composition, said kit comprising

(i) a first vessel containing the composition in a first condition and being closed by a rupturable seal;

(ii) a second vessel containing a medium for conversion of the composition from the first condition to a second condition, said second vessel being closed by a rupturable seal; and

(iii) a connector member onto which said first and second vessels are assemblable, said connector member being adapted to rupture said seals and to provide for communication of the interiors of said first and second vessels.

In the kit of the invention, conversion of the composition from its first condition to its second condition may be effected by assembling the first and second vessels onto the connector. This action causes rupture of the seals to provide for communication between the interiors of the first and second vessels which are held together by the connector member. Consequently the contents of one vessel may be transferred to the other so that the medium originally present in the sealed second vessel is capable of effecting conversion of the composition from its first condition (as originally sealed in the first vessel) to a second condition.

Various types of conversion are contemplated by the present invention. Examples include resuscitation, dehydration, extraction and other treatment processes.

The invention is applicable particularly to the storage of microorganisms in an inactive (suspended) form and their resuscitation into an active form. In this case, the composition sealed in the first vessel will comprise the inactivated microorganisms and the composition sealed in the second vessel may be a resuscitation liquid.

The micro-organisms may be bacteria or viruses. The suspended microorganisms may be supported on a solid support, e.g. beads.

The invention is however also applicable to the storage and conversion of other compositions, e.g. vaccines. A further possibility is the storage and conversion of enzymes. Thus the enzyme may be stored in a dried form in one of the vessels the other vessel containing a diluant. The enzyme may, for example, be Alkaline Phosphatase and the diluant may be a buffer solution. A still further possibility is the treatment of a sample, to extract a component thereof, for the purposes of analysis.

In an embodiment of the invention, the first or second vessel may comprise an additional rupturable seal of the type described and that vessel may additionally be connectable to a third vessel (with its own rupturable seal) by a further connector member as described. Such an assembly may be used, for example, for the analysis of samples, e.g. to detect the presence or otherwise of a component of interest therein. The first vessel may contain the sample to be analysed, the second vessel with two rupturable seals may contain process chemicals and the third may contain chemicals for detection. Initially the contents of the first and second vessel are mixed as a result of rupture of the appropriate seals by the connector member connecting these two vessels together. Subsequently the seal between the second and third vessels are ruptured to allow mixture of the sample/processing chemicals admixture with the detection chemicals which might, for example, provide a colour change of the component of interest was present in the sample.

Clearly four or more vessels could be provided in accordance with the principal of construction outlined in the previous paragraph.

Conveniently for all embodiments of the invention the vessels and connector are formed of plastics materials. The vessels may, for example, be of polypropylene (preferably a homopolymer) and may have a wall thickness of at least 1.5mm. The connector may, for example, be of polyethylene.

In a preferred embodiment of the invention, the connector is such that the first and second vessels as assembled thereon are in axial alignment. Rupture of these seals is then effected by movement of the vessels axially inwardly of the connector. Most preferably the vessels and the connector have complementary screw-thread formations whereby rotation of the vessels relative to the connector effects said relative axial inward movement.

The connector may comprise a bore into which the mouths of the first and second vessels are inserted at opposite ends and said bore may include a transverse partition provided on either side with formations for effecting rupture of the seals of the first and second vessels, said formations being associated with a passageway in the partition allowing for communication of the interiors of said vessels once these seals have been ruptured.

The rupturable seals of the first and second vessels may be of a flexible material which is sealed across the mouths of the vessels once the respective contents have been provided therein. The seal may for example be of metal (e.g. aluminium foil), a plastics material or a laminate of such materials. The seal may be bonded to the vessels by means of an adhesive or, more preferably, by ultrasonic welding.

In an embodiment of the invention described in the previous paragraph, the material of the seal is provided over the aperture of a ring (and preferably bonded thereto by ultrasonic welding) and said ring is preferably an interference fit in the mouth of the vessel.

For preference the ring is an interference fit in the mouth of the vessel and preferably also is ultrasonically welded thereto. Preferably also the seal is ultrasonically welded thereto.

It is however more preferred that at least one of the vessels of the kit is closed by a plug (which may be of a relatively rigid plastics material) comprising a tubular

body portion locating within the vessel and an integral cap which provides the rupturable seal. Such a construction provides a second aspect of the invention according to which there is provided a kit for the storage and conversion of a composition, said kit comprising

(i) a first vessel containing the composition in a first condition, said vessel being closed by a plug comprising a tubular body portion locating within the vessel and an integral cap which provides a seal;

(ii) a second vessel containing a medium for conversion of the composition from the first condition to a second condition, said vessel being closed by a plug comprising a tubular body portion locating within the vessel and an integral cap which provides a seal; and

(iii) a connector member onto which said first and second vessels are assembleable, said connector member being adapted to breech said seals and to provide for communication of the interiors of said first and second vessels.

The or each cap may be formed with a line of weakness for rupture of the seal by the connector member. The line of weakness is preferably defined by a groove. The groove is preferably circular and is most preferably provided on the under-surface of the cap.

Conveniently, the rupture of the seals is effected by virtue of the connector member exerting a severing action on the cap (of the plug) in the region of the groove (or other line of weakness). Thus, for example, formations in the connector for effecting rupture of the seals may have end faces which are slanted (e.g. at an angle of 20-25^{O}) relative to the transverse cross-sectional plane of the connector. Given that the groove (or other line of weakness) is circular, the distance across an end face of the formation may correspond to the diameter of the groove. Rotation of the formations relative to the seal causes a rotary severing action around the groove.

It is particularly preferred that the plug is of polycarbonate since this material will fracture (rather than stretch) to provide for rupture of the seal.

It is particularly preferred that the body portion of the plug is an interference fit within the mouth of the vessel.

A further aspect of the invention relates to sealed vessels of the type described above. Such sealed vessels may, for example, contain inactivated micro-organisms, resuscitation liquids therefor, an inactivated form of a vaccine (e.g. antibodies/antigens/conjugates), an activating liquid therefor, a dried enzyme (e.g. Alkaline Phosphatease), a diluant (e.g. a buffer) therefor, antibiotics, nucleic acids (e.g. RNA or DNA), buffers therefor, dried cells etc.

Further aspects of the invention provide the combination of a vessel and its rupturable seal. A further aspects provides the combination of the vessel, its rupturable seal and the connector member.

The invention will be described by way of example only with reference to the accompanying drawings, in which:

Fig 1 illustrates the components of a first embodiment of activation kit in accordance with the invention;

Fig 2 is a detail of Fig 1 but showing the parts thereof in an assembled condition;

Fig 3 illustrates a vessel for use in the kit shown in Fig 1; and

Fig 4 illustrates a modification of one of the kit components of Fig 1;

Fig 5 is an axial sectional view to an enlarged scale of a kit in accordance with the second aspect of the invention;

Figs 6a-c are sectional views of one of the vessels of the kit section shown in Fig 5 and its associated plug;

Fig 7 is a sectional view of the connection of the kit illustrated in Fig 5;

Figs 8a and 8b illustrate the manner in which the seals of the vessels shown in Fig 5 are ruptured; and

Fig 9 illustrates a further embodiment of the second aspect of the invention.

Referring firstly to Fig 1, the illustrated kit 1 comprises two cylindrical vials 2 and 3 as well as a cylindrical connector 4.

Vial 2 has an external screw thread formation 5 adjacent the mouth of the vial, which mouth is closed by a seal 6 in the form of a disc of a puncturable material for example be in the form of a laminate of aluminium and plastics foils. The seal 6 may be bonded to the end of the vial 2 by means of an adhesive.

Vial 3 is of the same construction as vial 2 but for convenience its screw-thread formation and seal are referenced as 7 and 8 respectively.

Connector 4 is generally hollow and at each end has internal screw-thread formations 9 and 10 which are respectively complementary to the screw thread 5 and 7 of the two vials. Provided midway along the bore of connector 4 is a transverse partition 11 having to axially projecting noses 12 and 13 with there being an axial passageway 14 extending wholly through the partition 11 from one nose to the other.

In the illustrated embodiment, vial 2 is shown as containing a plurality of beads 15 on which are supported microorganisms (e.g. bacteria, not shown) that are preserved in a dry suspended state for example by means of freeze drying. The microorganisms may be packaged in the vial 2 by use of the techniques described

more fully in our co-pending UK Patent Application No. 0009993.7 filed on 26th April 2000.

Vial 3 contains a liquid 16 capable of resuscitating the microorganisms.

When it is desired to re-activate the microorganisms, the mouths of vials 2 and 3 are screwed into opposite ends of the connector 4 (as illustrated in the detail of Fig 2).

The act of screwing vial 2 into the connector 4 has the effect of bringing the vial's seal 6 into proximity with the nose 12 (see the detail of Fig 2). Similarly for the vial 3 save that its seal 8 approaches nose 14. Once the vials have been screwed past a particular point, their respective seals are ruptured by the adjacent nose. This is illustrated in Fig 2 for vial 3.

It will thus be appreciated that the action of screwing the vials 2 and 3 into the connector 4 results in rupture of the two seals 6 and 7. The assembly may now be orientated so that the resuscitation liquid 16 is transferred from vial 3 *via* passageway 14 into vial 2 for reactivation of the microorganisms provided therein.

It will be appreciated that the components (i.e. the vials 2 and 3 with their respective contents and the cylindrical connector 4) of the activation kit shown in Fig 1 may be supplied to an end user in a vacuum pack which is thus a "self-contained" unit of inactivated microorganism, resuscitation liquid, and means for causing the resuscitation of the microorganisms. In such a pack, the vials 2 and 3 may be partially screwed into connector 4 (but not so far as to cause rupture of the seals 4 and 6). Alternatively, the three components may be supplied, in the pack, in "disassembled" form for assembly as described more fully above.

Reference is now made to Fig 3 which illustrates a method of providing a sealed vial for use in the kit illustrated in Fig 1. More particularly, Fig 3 illustrates a vial 30 whereof the mouth is closed by a closure element 31 itself comprised of a rigid

plastics ring 32 whereof the central aperture 32a is closed by a rupturable seal 33. In more detail, the seal 33 is comprised of a laminate of aluminium foil 33a and a plastics material 33b. In the assembled closure element 31, the plastics layer 33b (of seal 33) is ultrasonically welded to the ring 32.

Further, as illustrated in Fig 3, ring 31 is of generally frustoconical section and locates as an interference fit in the mouth of vial 30 which (again as illustrated) is of a frustoconical formation complementary to that of ring 32. With the closure element 31 located in position in the mouth of vial 30, it is finally sealed in position by ultrasonic welding.

The arrangement shown in, and described with reference to, Fig 3 may be used for one, other or both of the vials 2 and 3 illustrated in Fig 1.

Whilst the kit of Fig 1 has been described with reference to storage and resuscitation of inactivated microorganisms other applications are possible. Thus, for example, one of the vials 2 or 3 may contain an inactivated form of a vaccine and the other may contain an activating liquid therefor. In this case, the embodiment of Fig 4 has particular application. In this embodiment, the base of one of the vials is provided with a septum arrangement 40 through which the needle of a hyperdermic syringe or the like may be inserted for withdrawal of the activated vaccine.

Reference is now made to the kit and the components thereof as illustrated in Figs 5-8 of the drawings. It can seen from the axial section of Fig 5 that the kit 101 illustrated therein is generally similar to that of Fig 1 to the extent that it comprises two cylindrical vials 102 and 103 as well as a cylindrical connector 104. The vials 102 and 103 are adapted to screw into opposite ends of the connector 104 in the same way as the vials 2 and 3 screw into the connector 4.

Vials 102 and 103 do however differ from the vials 2 and 3 (of Fig 1) with regard to the manner in which the rupturable seal is provided.

As shown in Fig 5, each of vials 102 and 103 is closed by a plug 105 or 106 respectively which will now be described (for vial 102 and its plug 105) with reference to Figs 6a-c.

As shown in the sectional scrap view to Figs 6a-c, the plug 105 is a one-piece component and comprises a generally cylindrical body 107 closed at its upper end by an integral cap 108. The body 107 of the plug 105 is an interference fit in the top of vial 102 and, when pushed home, locates therein in the manner shown in Fig 6c with an annular lip 110 of the cap 108 engaging against the upper rim 109 of the vial 102.

The underside of cap 108 is formed with an annular, downwardly opening V-sectioned grooved 110 located immediately radially inwardly of the inner wall of the cylindrical body 107. By virtue of the presence of groove 110, there is an annular region (represented by reference numeral 112) of the cap 108 where the material thereof is of reduced thickness as compared to the remainder of cap 108. This reduced thickness annular region 112 bounds a central portion 113 of the cap 108.

The construction of vial 103 and its plug 106 is exactly as described above for vial 102 and plug 105.

When it is desired to provide a vial 102 with a sample of micro-organism in an inactive (suspended) form then the following procedure is adopted. Initially, the "live" micro-organism is introduced into the vial 102 prior to location of the plug 105 thereon. Subsequently, plug 105 is positioned so as to rest on the top of vial 102 in the manner illustrated in Fig 6b. The plug 105 remains on top of vial 102 by virtue of the fact that it is an interference fit therein. The assembly of the vial 102 and its plug 105 (as illustrated in Fig 6b) may be subject to freeze drying (lyphilisation) under vacuum conditions. A small "gap" that exists between the lower edge of the plug 105 and the upper rim of vial 102 is sufficient to allow freeze drying of the micro-organism culture in the vial 102.

Subsequently, the plug 105 is pushed home into the mouth of the vial 102 (see Fig 6c).

Vial 103 is fitted with its plug 106 in a similar manner (after vial 103 has been provided with its content, e.g. resuscitation solution).

Reference is now made to Fig 7 which illustrates connector 104 in more detail. Essentially, the cylindrical connector 104 is similar to the connector 4 (as described and illustrated with reference to Figs 1 and 2) but the axially projecting noses 114 and 115 have their annular end faces formed in a plane at an angle to the diametral plane of the connector 104. This angle may, for example, be about 20-25 (e.g. about 23) degrees.

Assembly of the kit 101 is similar to assembly of the kit 1 as described and illustrated with reference to Fig 1. In other words, the vials 102 and 103 are screwed into the connector 104. However in the case of the kit 101, the leading edges of angled faces of the noses 112 and 113 serve to exert a severing action on the cap 108 (of the plug 105) in the region of the annulus 112 of reduced thickness. As a result of this severing action, and in combination with the axial movement of the vials 102 and 103 relative to the connector 104, the central portions 113 become detached (see Fig 8) so that the interiors of vials 102 and 103 communicate with each other.

Conveniently the caps 105 and 106 are of polycarbonate since this material fractures rather then stretches. The connector 104 may be of polyethylene and the vials 102 and 103 may be of polypropylene (preferably homopolymer). A wall thickness of at least 1.5mm is generally suitable for the vials 102 and 103.

In a modification of the arrangement shown in Fig 5, one of the vials 102 and 103 may be provided with a septum in the manner illustrated in Fig 4.

Fig 9 shows an embodiment of the invention which is a modification of that shown in Fig 5. More particularly, the embodiment of Fig 9 comprises vessels 102

and 103 of the construction illustrated in, and described for, Fig 5 but there being an intermediate vessel 120 provided at opposite ends with plugs 121 and 122 (which are of exactly of the same construction as described for the plugs 105/106 of Fig 5. Two connector members 123 and 124 (both identical to connector member 104) are provided as shown, one for connecting the vessels 102 and 120 (and rupturing their respective plugs 105 and 121) and the other connecting vessels 120 and 103 (and for rupturing their respective plugs 122 and 106).

Vessel 102 may, for example, contain a sample to be analysed. Vessel 120 may contain processing chemicals for the purposes of extracting a component of interest from the sample. Vessel 103 may contain detection chemicals. Initially vessels 102 and 120 are rotated relative to their connector 123 to rupture the seals in their respective caps 105 and 121. The contents of vessels 102 and 120 may now be mixed to treat the sample. Subsequently the vessels 103 and 120 are rotated relative to their connector 124 to rupture the seals associated with their respective plugs 122 and 106. The treated sample may now be mixed with the detection chemicals from vessel 103.

CLAIMS

1. A kit for the storage and conversion of a composition, said kit comprising

(i) a first vessel containing the composition in a first condition and being closed by a rupturable seal;

(ii) a second vessel containing a medium for conversion of the composition from the first condition to a second condition, said second vessel being closed by a rupturable seal; and

(iii) a connector member onto which said first and second vessels are assembleable, said connector member being adapted to rupture said seals and to provide for communication of the interiors of said first and second vessels.

2. A kit as claimed in claim 1 wherein the connector is such that the first and second vessels as assembled thereon are in axial alignment and rupture of the seals is effected by axial movement of the vessels relatively inwardly of the connector.

3. A kit as claimed in claim 2 wherein the vessels and connector have complementary screw-thread formations whereby rotation of the vessels relative to the connector effects said relative axial movement.

4. A kit as claimed in any one of claims 1 to 3 wherein the connector comprises a bore into which the mouths of the first and second vessels are inserted at opposite ends and said bore includes a transverse partition provided with formations for effecting rupture of the seals of the first and second vessels, said formations being associated with a passageway in the partition allowing for communication of the interiors of said vessels once the seals have been ruptured.

5. A kit as claimed in claim 4 wherein said formations comprise noses on opposite sides of the partitions and said passage way extends axially through the noses.

6. A kit as claimed in any one of claims 1 to 5 wherein the vessels and connector are of plastics material.

7. A kit as claimed in any one of claims 1 to 6 wherein the seals of the first and second vessels are of a flexible material.

8. A kit as claimed in claim 7 wherein the seals are of metal foil, plastics or a laminate of such materials.

9. A kit as claimed in any one of claims 1 to 6 wherein at least one of the vessels is closed by a plug comprising a tubular body portion locating within the vessel and an integral cap which provides the rupturable seal.

10. A kit as claimed in claim 9 wherein the or each cap is formed a line of weakness for rupture of the seal by said connector member.

11. A kit as claimed in claim 10 wherein the line of weakness is a circular groove.

12. A kit as claimed in claim 11 wherein the groove is provided on the under surface of the cap.

13. A kit as claimed in any one of claims 9 to 13 wherein the body portion of the plug is an interference fit within the vessel.

14. A kit as claimed in any one of claims 9 to 13 wherein the plug is of polycarbonate.

15. A kit as claimed in any one of claims 1 to 14 wherein the connector member is of polyethylene.

16. A kit as claimed in any one of claims 1 to 15 wherein the vessel is of polypropylene.

17. A kit for the storage and conversion of a composition, said kit comprising

(i) a first vessel containing the composition in a first condition, said vessel being closed by a plug comprising a tubular body portion locating within the vessel and an integral cap which provides a seal;

(ii) a second vessel containing a medium for conversion of the composition from the first condition to a second condition, said vessel being closed by a plug comprising a tubular body portion locating within the vessel and an integral cap which provides a seal; and

(iii) a connector member onto which said first and second vessels are assembleable, said connector member being adapted to breech said seals and to provide for communication of the interiors of said first and second vessels.

18. A kit as claimed in claim 17 wherein the connector comprises a bore into which the mouths of the first and second vessels are inserted at opposite ends and said bore includes formations for effecting breech of the seals of the first and second vessels, said formations being associated with a passageway in the partition allowing for communication of the interiors of said vessels once the seals have been breeched.

19. A kit as claimed in claim 18 wherein the seals include a line of weakness and said formations exert a severing action on the line of weakness.

20. A kit as claimed in claim 18 or 19 wherein said formations comprise noses and said passageway extends axially through the noses.

21. A kit as claimed in any one of claims 1 to 8 wherein the seals are mounted on, and close the apertures of, rings located in the mouths of the vessels.

22. A kit as claimed in claim 21 wherein each ring is ultrasonically welded to the body of the respective vessel.

23. A kit as claimed in claim 21 or 22 wherein the seal is ultrasonically welded to the ring.

24. A kit as claimed in any one of claims 1 to 23 wherein at least the first or second vessel is provided with a septum.

25. A kit as claimed in any one of claims 1 to 24 wherein the first vessel contains inactivated microorgansims and the second vessel contains a resuscitation liquid therefor.

26. A kit as claimed in any one of claims 1 to 24 wherein the first vessel contains an inactivated vaccine and the second vessel contains an activation liquid therefor.

27. A kit as claimed in any one of claims 1 to 24 wherein the first vessel contains a dried enzyme and the second vessel contains a diluant therefor.

28. A kit as claimed in claim 27 wherein the enzyme is Alkaline Phosphatase and the diluant is a buffer.

29. A kit as claimed in any one of claims 1 to 28 wherein at least one of the first and second vessel comprises an additional rupturable seal and that vessel is additionally connectable to a third vessel with its own rupturable seal by a further connector member.

30. A sealed vessel whereof the mouth of the vessel is closed by plug comprising a tubular body portion locating within the vessel and an integral cap which provides a seal, said cap being provided with a line of weakness facilitating breech of the seal.

31. A vessel as claimed in claim 30 wherein the line of weakness is provided by a groove in the cap.

32. A vessel as claimed in claim 31 wherein the groove is circular.

33. A sealed vessel whereof the mouth of the vessel is closed by a ring provided with a rupturable seal.

34. A vessel as claimed in 33 wherein the ring is an interference fit in the mouth of the vessel.

35. A vessel as claimed in claim 33 or 34 wherein the ring is ultrasonically welded to the mouth of the vessel.

36. A vessel as claimed in any one of claims 34 to 35 wherein the rupturable seal is ultrasonically welded to the ring.

37. A vessel as claimed in any one of claims 30 to 36 containing inactivated micro-organisms, resuscitation liquid therefor, an inactivated form of a vaccine, an activating liquid therefor, a dried enzyme, a diluant therefor, antibiotics, nucleic acids, buffers therefor or dried cells.

38. A vessel containing an inactivated form of a microorganism and having a seal of a flexible, rupturable material.

39. A vessel containing a resuscitation liquid for an inactivated microorganism and having a seal of a flexible rupturable material.

40. The combination of a vessel having a mouth and a plug comprising a tubular body portion for location within the vessel and an integral cap which provides a seal, said cap being provided with a line of weakness facilitating breach of the seal.

41. The combination as claimed in claim 40 wherein the line of weakness is provided by a groove in the cap.

42. The combination as claimed in claim 41 wherein the groove is circular.

43. The combination as claimed in any of claims 40 to 42 which comprises two of said vessels, two of said plugs and which further comprises a connector member onto which said vessels with plugs fitted are assemblable, said connector member being adapted to breach said seals and to provide for communication of the interiors of said first and second vessels.

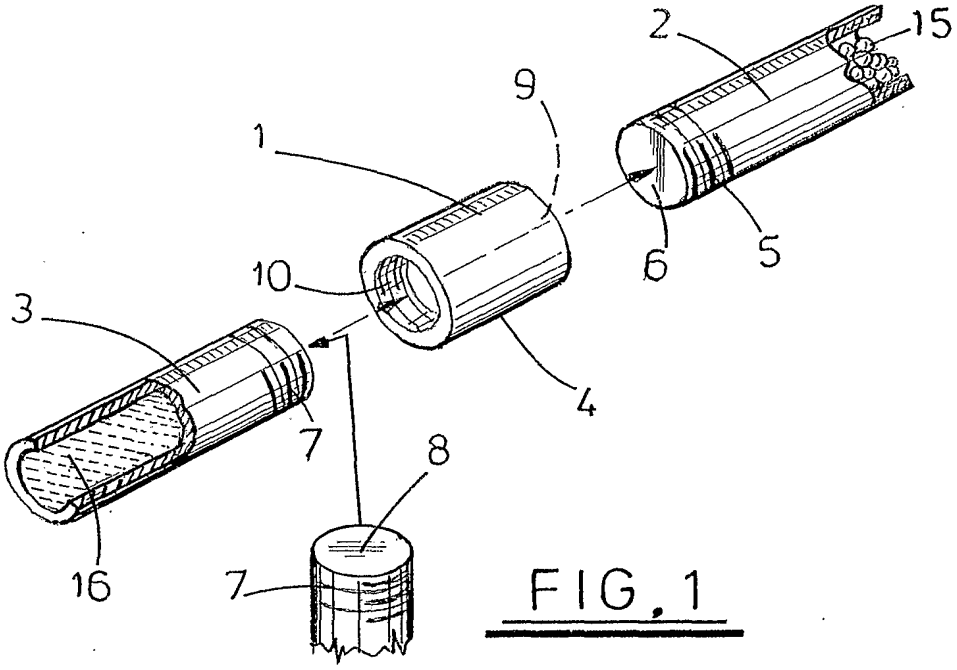

FIG. 1

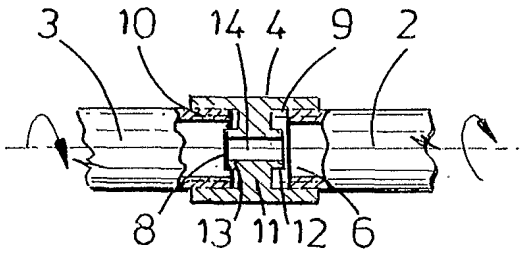

FIG. 2

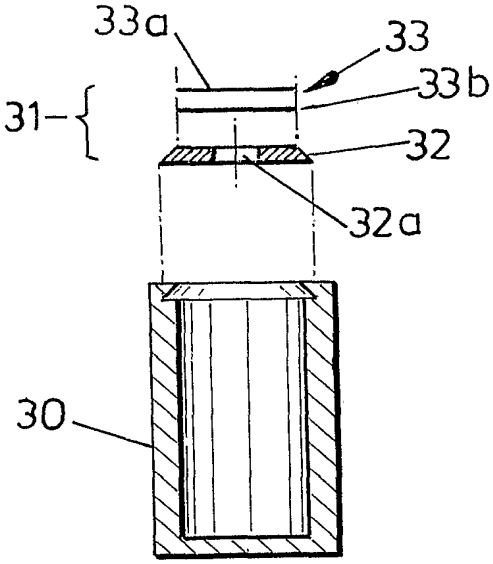

FIG. 3

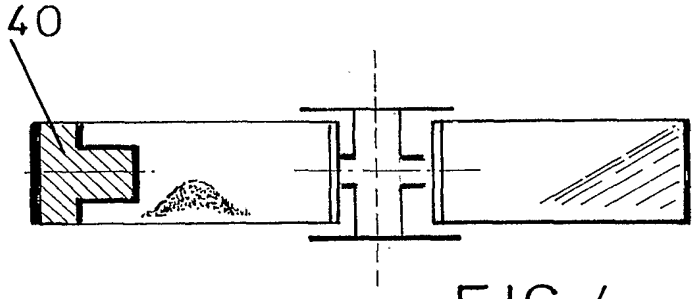

FIG. 4

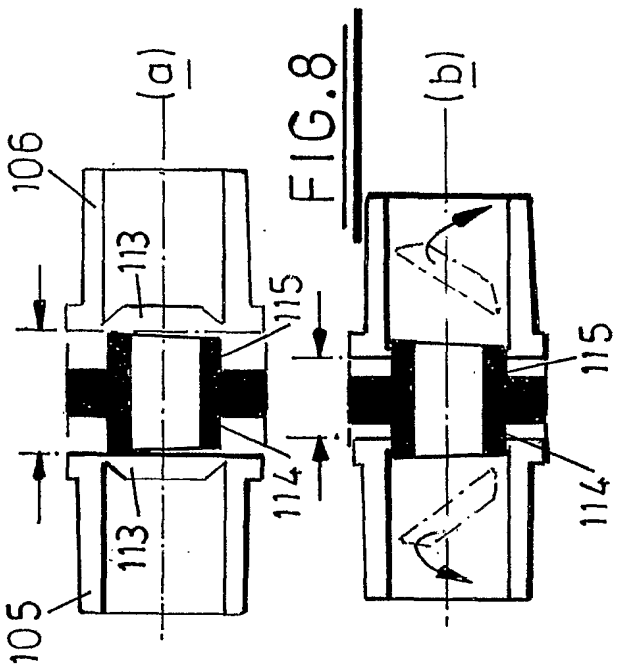

FIG.8

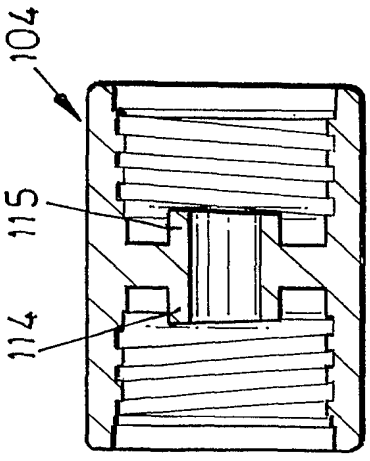

FIG.7

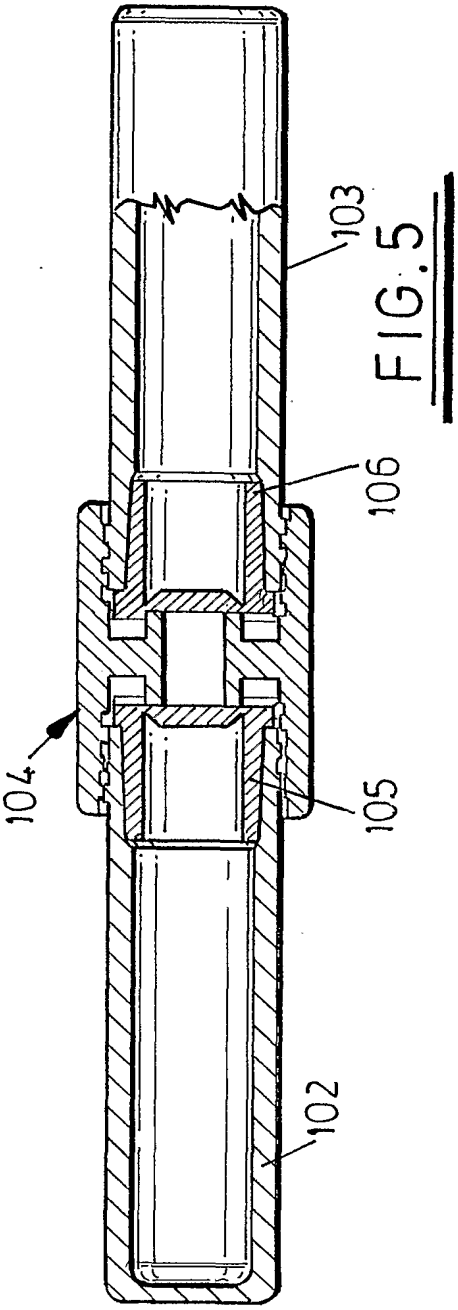

FIG.5

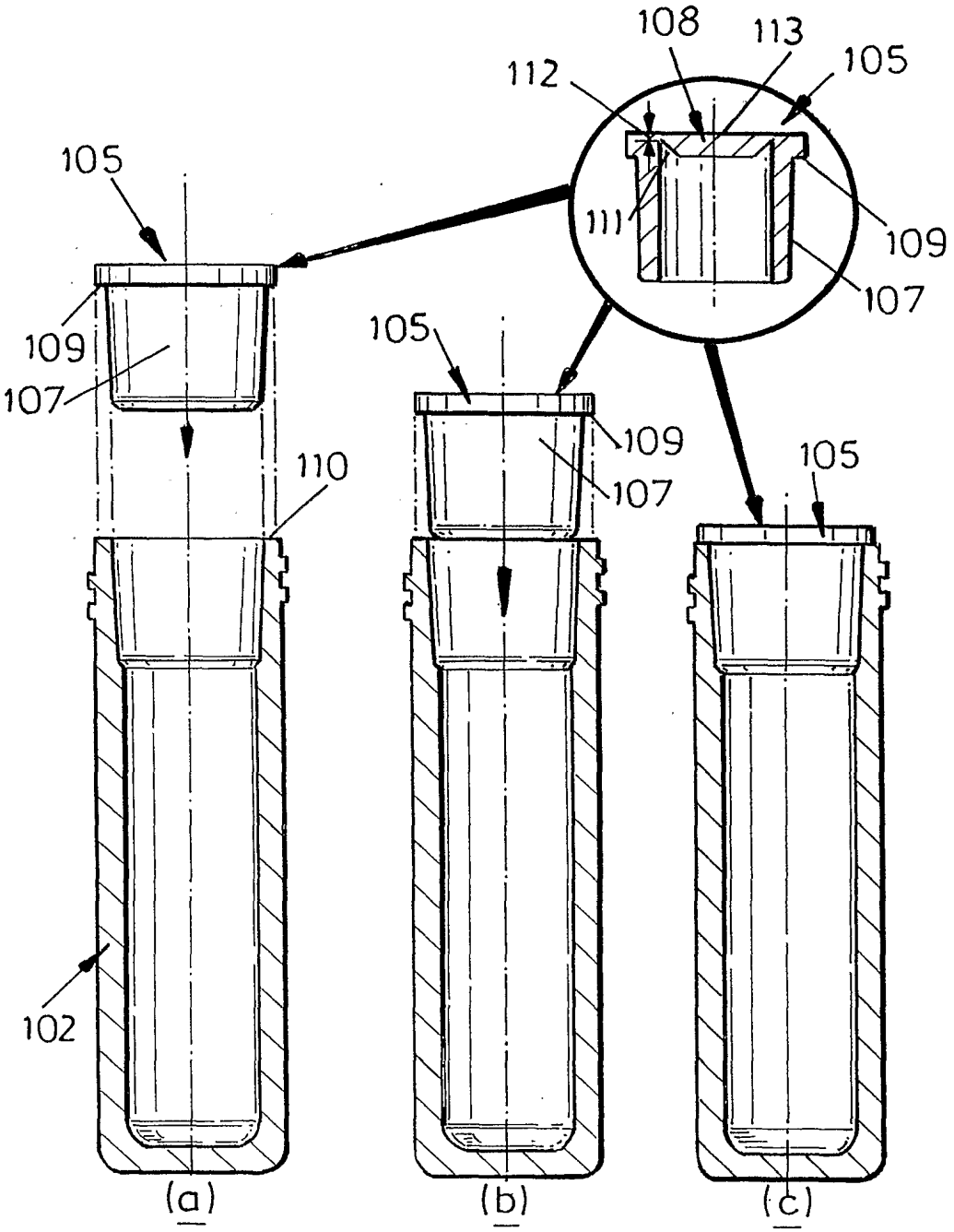
108
113
105
112
105
111
109
107
109
107
105
109
107
105
110
102
(a)
(b)
(c)

FIG. 6

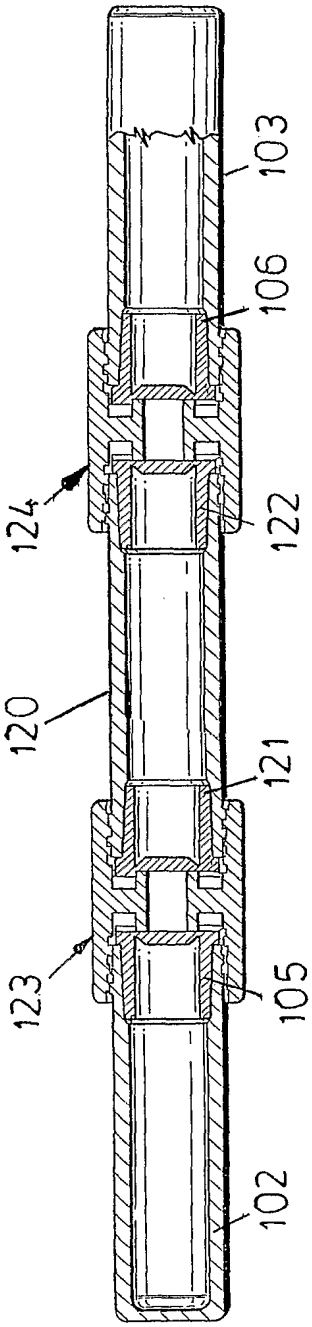

FIG. 9